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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/346,794	07/02/1999	TERRY P. SNUTCH	NMEDP001-2	2888

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EXAMINER

BASI, NIRMAL SINGH

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/346,794

**Applicant(s)**

SNUTCH ET AL.

**Examiner**

Nirmal S. Basi

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 25-31 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 3/26/04.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 3/26/04 has been entered. The finality of the previous Office Action is withdrawn.

2. Amendment filed 3/26/04 has been entered.

3. Applicants argue there remain two outstanding issues. One the Office may not properly restrict between the three nucleic acid sequences specified in each independent claim. The second is whether the claims have utility and whether the specification enables their use in accordance with 35 U.S.C. 101 and 112, first paragraph. Applicants argue the claimed methods have well-established, specific, substantial and credible utilities and the specification teaches such uses. Applicants arguments have been fully considered but not found persuasive, and are addressed below.

#### **Examiner's Response to Applicants' Arguments Pertaining to Restriction Requirements.**

4. Claims 25-31 are pending. Applicants elected the species of SEQ ID NO: 23 (January 31, 2003). Applicants' election was in response to the Office Action mailed 31 December 2002. Applicants argue the Office action mailed May 6,

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2003 stated that the species election requirement was meant to be constructed as a restriction requirement and made the requirement final. Applicants further argue the Office deemed for the first time in the Office action mailed May 6, 2003 that the election of SEQ ID NO:23 was a requirement for restriction, therefore making the restriction requirement final was improper. It is requested the finality of the restriction requirement in the Office action mailed May 6, 2003 be withdrawn. It is also argued that there is no undue search burden on the Office when performing a database search for the pending claims. In the paper filed 3/26/04 Applicants provisionally elected, with traverse, claims directed to the use of the  $\alpha 1$  subunit species encoded by a nucleotide sequence that hybridizes to a nucleic acid comprising SEQ ID NO: 23, and request reconsideration of the restriction requirement.

Applicants' arguments have been fully considered but not found persuasive for the reason given below. The claims were properly restricted between the three nucleic acid sequences specified in each independent claim. Examiner has briefly recited the timeline of Restrictions imposed by the office and also indicated Applicants responses:

On 10/4/00, Office mailed Restriction requirement

On 12/8/200, Applicants elected Group XVI, claim 21, directed to a screening method.

On 10/8/02 Applicant amended the pending claims, to overcome Examiner's rejections. Applicants amended the claims to read on a method for identifying a compound which behaves as an agonist for a T-type calcium

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channel which is encoded by a nucleotide sequence which hybridizes to a nucleic acid comprising SEQ ID NO:23, 25, or 27.

On 31 December, 2002, in response to Applicant's Amendment, the Examiner further restricted the claims. The office action specifically stated, "The nucleic acid comprising SEQ ID NO: 23, 25 or 27 are three distinct classes of calcium channel subunits and constitute recitation of an implied, mis-joined Markush group that contains multiple, independent and distinct inventions. Each of the different nucleic acids encode a distinct polypeptide with distinct structural or functional properties and therefore the methods of their use are independent and distinct". It was also stated, **"This requirement is not constructed as a requirement for election of species since each of the compounds recited in alternative form is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention,**

On 2<sup>nd</sup> February, 2003, Applicant elected SEQ ID NO:23 with traverse. The Examiner further stated, " The previous restriction requirement was not meant to be constructed as a requirement for election of species". Therefore, further emphasizing the requirement, **"This requirement is not constructed as a requirement for election of species since each of the compounds recited in alternative form is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention"**, as stated in the previous Office action.

On May 6, 2003 the Examiner acknowledged Applicants election, with traverse, of the species of nucleic acid comprising SEQ ID NO:23. Applicants'

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arguments were fully considered but not found persuasive. The requirement was deemed proper and therefore made FINAL.

Based on the above responses by the Office restriction was proper.

Therefore, the use of each individual nucleic acid comprising SEQ ID NO:23, 25 or 27 is considered distinct. Therefore, the restriction requirement is not to be construed as a requirement for election of species, since each of the compounds recited in alternative form is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention; therefore the use of each member in a method also constitutes an independent and patentably distinct invention. The claims of elected Group XVI are drawn to a method to identify a compound which behaves as an agonist or an antagonist for a T-type calcium channel by contacting the  $\alpha_1$  subunit of a heterologous T-type calcium channel with a compound, wherein said  $\alpha_1$  subunit is encoded by a nucleotide sequence which hybridizes (under conditions of specific stringency) to a nucleic acid comprising SEQ ID NO:23, 25 or 27. The claims apply to numerous T-type calcium channel  $\alpha_1$  subunits. The nucleic acid comprising SEQ ID NO:23, 25 or 27 are three distinct classes of calcium channel subunits, each an independent and distinct invention. Each of the different nucleic acids encodes distinct polypeptides with distinct structural or functional properties, each one with different agonist or antagonist binding properties. Agonists or antagonists identified, for example, by the use of the polypeptide encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO:23, may not be the same as those identified by the polypeptide encoded by a nucleotide, which

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hybridizes to the nucleic acid of SEQ ID NO:25 or 27. The nucleic acids comprising SEQ ID NO:23, 25 and 27 were grouped into distinct Groups III, IV and V respectively, in paper number 8 (10/4/000). Therefore, the use of each individual nucleic acid comprising SEQ ID NO:23, 25 or 27 is also considered distinct. The nucleic acids of Groups III-V are distinct for reasons of record, see paper number 8. Accordingly, these claims are subject to restriction under U.S.C. § 121. Further a search of SEQ ID NO:23, 25 and 27 and all the possible nucleic acids that would hybridize to said nucleic acid and encode a T-type calcium channel would not be co-extensive particularly with regard to the literature search. An examination of the materially different, patentably distinct inventions in a single application would constitute a serious undue burden on the examiner. The requirement is still deemed proper and is therefore still FINAL.

***Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph***

The following is a quotation of 35 U.S.C. 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the

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same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### **Examiner's Response to Applicants' Arguments Pertaining to Rejection**

#### **Under, 35 U.S.C. 101 and 112, first paragraph**

5. Claims 25-31 remain rejected, under 35 U.S.C. 101 and 112, first paragraph, for reasons of record in the Office Action dated 5/6/03, 2/7/02 and for the reasons given below.

Applicants' arguments are summarized below.

Applicants' argue:

1. The  $\alpha_1$  subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23, 25 or 27 are functional full-length subunits and the specification teaches a person of ordinary skill in the art how to use the specified  $\alpha_1$  subunit in screening assays.

2. Publications at the time the priority application was filed demonstrate T-type calcium channel assays had a well-established utility as they were useful for identifying compounds that treat diseases such as hypertension, stroke, epilepsy, heart disease and cancer.

3. A declaration submitted by Dr. Snutch, which must be considered by the Office, demonstrates the claimed screening methods are useful for identifying molecules that treat T-type calcium channel related diseases.

4. Due to the facts delineated in items 1, 2 and 3, the screening assays have a well-established, specific, substantial and credible utility for



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identifying compounds useful for treating diseases enumerated in the specification.

5. Little or no experimentation is required beyond the claimed processes to identify compounds that treat diseases listed in the specification.

6. The Office already has allowed claims directed to T-type channels, proving that claims directed to their use have utility.

Applicant further argues:

a) The  $\alpha_1$  subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NOs: 23, 25 or 27 form functional full-length calcium channels. Although the properties of these channels may be modulated by co-expression of other subunits, the  $\alpha_1$  subunits alone are functional. The specification states the  $\alpha_1$  subunits are by themselves T-type calcium channels and teaches the person of ordinary skill in the art how to make recombinant cells utilized in the claimed methods. The specification also teaches methods of using such receptors and recombinant cells in standard methods for screening agonists and antagonists. The specification teaches cell lines expressing  $\alpha_1$  subunits can be used to evaluate the effects of pharmaceuticals and/or toxic substance on calcium channels. The specification also teaches that the calcium channel subunit may be associated with human genetic diseases, the logical conclusion is the agonists and antagonists identified by the claimed screening assays are expected to be useful for treating these diseases. The diseases include epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease. Thus,

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the specification teaches the claimed processes are useful for identifying agonists and antagonists of T-type calcium channels and diseases associated with such channels.

b) Prior art shows that T-type calcium channel agonists were useful for treating a number of diseases set forth in the specification. Thus, the utility of T-type calcium channel screening assays for identifying therapeutic molecules was well established before the priority application was filed.

c) A compound that binds to one T-type calcium channel binds to all T-type calcium channels. Therefore a compound that treats a disease by binding one T-type channel will bind another T-type calcium channel and exert an effect due to the sequence homology between these channels. As it is well-established there are known T-type calcium channel antagonists useful for treating diseases listed in the specification, the claimed methods have utility for identifying therapeutic molecules. The invention claimed is a method to identify agonists and antagonists of the calcium ion channels and there is no assertion that the channels themselves or the nucleotides encoding them are candidates as pharmaceuticals for treating diseases, it is the agonists or antagonists of these channels which have an effect on the activity of the endogenous calcium ion channels in a subject to be treated. Thus, the link between the claimed screening assays and the utility of agonists identified by the assays for treating T-type channel-associated diseases is clear.

d) The claimed screening assays have a well-established, specific, substantial and credible utility. The utility is specific because the claimed

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screening assays are useful for identifying agonists and antagonists of the specified  $\alpha_1$  subunits. The utility is substantial as the agonists and antagonists identified by the screening methods have the real world use of treating diseases specified in the specification. The utility is credible because the applicants have generated recombinant cells according to the claimed specification and have screened multiple molecules that act as agonists or antagonists of the  $\alpha_1$  subunit. The utility also is credible because the publications submitted in Exhibits A through H demonstrate the usefulness of particular T-type calcium channel agonists for treating diseases. Further, the utility of the claimed screening methods is well established as evidenced by the state of the art before the filing date of the present patent application.

e) The claimed processes require little if no further experimentation for identifying agonists and antagonists useful for treating T-type channel-associated diseases. This feature is highlighted in the Snatch declaration and by journal articles published at the time and before the priority application was filed in 1997. As the use of the specified  $\alpha_1$  subunit in the claimed screening methods directly identifies compounds useful for treating the diseases set forth in the specification, the claimed subject matter is not merely a hunting license as compared to the technology at issue in *Brenner v. Manson*. Also, there is no requirement to determine whether new agonists and antagonists identified by the claimed assays in fact treat a disease in vivo in accordance with *In re Brana*, 34 USPQ.2d 1436 (Fed. Cir. 1995). Accordingly, there is little or no further experimentation required ascertaining whether the agonists or antagonists identified by the

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claimed assays are useful for treating diseases associated with aberrations in  $\alpha_1$  subunit.

f) The Office appears to have ignored the precedence of at least two patents that have issued directed to nucleotide sequences encoding T-type calcium channels. These patents are U.S. Patent Nos. 6,358,706 and 6,309,858. Based on the issuance of these patents the T-type calcium channels clearly are useful as presently claimed. Specifically, they are useful for identifying agonists and antagonists of calcium channel activity, which in turn are useful for treating a number of conditions. These utilities are exactly the same as those stated by the patentees in these issued patents. In addition, the Office has issued an entire litany of patents with respect to N-type calcium ion channels based on the same logic that applicants have been asserting in the present application. For example, U.S. Patent No. 6,096,514, U.S. Patent No. 6,090,626; U.S. Patent No. 6,013,474; and U.S. Patent No. 5,876,958

h) Accordingly, the claimed processes have a well-established, specific, substantial, credible and utilities as taught in the specification. As such, the applicants respectfully request that the Office withdraw the rejections under 35 U.S.C. 101 and 112, first paragraph.

The arguments presented in the Declaration of Snutch are disclosed below:

Snutch declares, the conditions associated with abnormal t-type calcium channel function are well established and agonists and antagonists of T-type calcium channels are useful in treating these conditions. There are several T-

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type calcium channels found in a single individual, which vary slightly in structure and demonstrably in terms of their distribution among various tissues. This, however, does not affect the usefulness of screening assays for agonists and antagonists. The particular T-type calcium channel involved in a particular condition may depend on its tissue distribution; for instance, T-type channels found in the nervous system are associated with epilepsy and neurological diseases in general where spastic convulsions are involved. However, it is not necessary to understand which particular T-type calcium channel is being used in a screen for compounds that would be useful in treating, for example, these convulsive conditions because of the similarity in the binding specificity of all T-type channels. In very simple terms, compounds which are found to inhibit or stimulate the activity of nervous T-type channels will also inhibit or stimulate the activity of T-type channels found in other tissues. Thus, any arbitrarily chosen T-type channel could be expressed in a cell line for use in screening assays to identify agonists or antagonists and the agonists or antagonists would be useful in treating the conditions associated with any T-type channel. As noted above, abnormal T-type activity is associated with a number of cardiac conditions, with hypertension, with neurological diseases involving spastic convulsions, and with impaired fertility. An agonist or antagonists identified with regard to any T-type channel would be useful in any and all of these conditions.

This pattern of similar binding activity among all T-type channels can be analogized to such a pattern among L-type channels. All of the T-type channels have similar behaviors in that they activate at low membrane potential, have

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small single channel conductance, have negative steady state inactivation properties, and contribute to spike firing patterns and rhythmic bursting processes. Analogous to the T-type channel another type of channel linked by similar behaviors is the L-type. There are several alpha subunits associated with various L-type channels, each is encoded by a distinct gene and exhibits a distinct distribution pattern. They can be discriminated from other types of calcium channels by their common sensitivity to 1,4-dihydropyridines. Thus, any one of these genes could be used to generate a L-type calcium channel for use in a cell-based assay to identify interacting compounds. These interacting compounds bind to all L-type channels and thus are useful in treating conditions related to any of them.

Applicants' arguments, the Declaration of Snutch and prior art references have been fully considered but not found persuasive for the reason given below. As an aside, it is noted that Terrance Snutch is one of the Inventors of the claimed invention and thus is a concerned party.

The ion channel encoded by the nucleic acid of SEQ ID NO:23 and the ion channels encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO:23, have not been disclosed to be involved in a specific disease state. There is no showing in the prior art or specification that the calcium channel subunit of SEQ ID NO:23 is the cause of any human genetic diseases. Further, there is no disclosure as to which T-type calcium ion channel, encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO:23, would be involved in the disease state of epilepsy, migraine, ataxia, schizophrenia,

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hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease. In fact, although the prior art and the Declaration of Snutch have suggested T-type calcium channels may be associated with or involved in disease states, there is no showing of a direct disease caused by dysfunction of a specific  $\alpha_1$  subunit of a T-type calcium channel.

There is no showing in the prior art or specification that agonists and antagonists identified by the claimed screening assays are useful for treating diseases including, epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease. Although the T-type calcium ion channel of SEQ ID NO:23 may be involved in one or more of the aforementioned disease states further experimentation is required to determine which disease state, if any, is a result of said T-type calcium ion channel dysfunction. Just because a nucleic acid hybridizes to the polynucleotide of SEQ ID NO: 23 it does not automatically mean it will encode a protein that will be involved in the aforementioned disease states. Again further experimentation is required to determine a function. Further, there is no disclosure of even a single agonist or antagonist identified by claimed method that will act as an antagonist or agonist to treat the diverse diseases claimed as possible targets. There is no disclosure of whether an agonist as compared to an antagonist will treat a specific disease. Therefore, further experimentation is required to find a compound that will bind to the T-type calcium ion channel used in instant methods and correlate it with a disease state.

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Claims 25-27 are directed to method for identifying agonists for a T-type calcium channel. Applicants have not disclosed a single agonist that has been identified by claimed method. Also the art provided by Applicants does not disclose a single compound that behaves as an agonist in the claimed method. Applicants have relied only on antagonists to argue utility.

Prior art does not disclose a utility for claimed invention, it argues to the contrary. The biophysical and pharmacological properties of T-type calcium channels are varied and their function is unknown. Although, the claimed method for identifying agonists and antagonists is considered useful by the Applicants, under 35 U.S.C. 101, they are not considered to have utility. What is the utility for method for identifying agonist and antagonist for a T-type  $\alpha_1$  subunit whose biophysical and pharmacological properties and function is unknown? The critical feature of the invention is the identification of compounds that activate or inhibit specific  $\alpha_1$  subunits of T-type  $\text{Ca}^{2+}$  channels. Since the  $\alpha_1$  subunits of T-type  $\text{Ca}^{2+}$  channels encoded by the polynucleotide of SEQ ID NO: 23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 are not considered to have utility under 35 U.S.C. 101, the method of their use is also are not considered to have utility.

The state of the prior art is disclosed in the review article of Sylvie et al (Sylvia et al, 1997, TIPS, Vol. 18, pages 37-42). Sylvie states, "Among  $\text{Ca}^{2+}$  channels, the low-voltage-activated T-type  $\text{Ca}^{2+}$  channel (T channel) is probably the most atypical. It was first described in 1984 and is found in a variety of cells where its precise role remains to be established. In addition, its molecular



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structure has never been defined, despite numerous attempts to sequence and clone it", page 37, first column. Sylvie does acknowledge that new drugs are being developed, which may block T-type channels. The drugs tested so far have not been shown to treat a single disease state, let alone the laundry list of diseases cited by applicants. Sylvie discloses the electrophysiological and pharmacological properties of T-type channels are varied (Table 1), and all T channels rarely meet the electrophysiological criteria (page 37, column 2). The effect of compounds on the ion channel is extremely dependent not only on the alpha-subunit but also on that of the associated beta-subunits (Sylvie et al, page 37, column 3). Therefore, the actions of compounds on T-type calcium channels depend on the molecular composition of the expressed channels and on the experimental conditions (Sylvie et al, page 37, column 3). The associated beta or other subunits required for a specific function of the T-type channel protein encoded by the nucleic acid of SEQ ID NO: 23 and the ion channels encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO: 23, in claimed method, are not disclosed. A compound that acts as an agonist or antagonist on the  $\alpha 1$  T-type channel protein used in claimed method may not have the same effect on other  $\alpha 1$  T-type channel proteins. For example  $Ni^{2+}$  blocks T channels, but as stated by Sylvie (page 37, column 3), "It is difficult to predict the actual potency of  $Ni^{2+}$  block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie also discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be

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useful (page 38, column 2). Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie et al, page 38, column 3). Further, compounds may have different effects depending on their concentration. For example, Sylvie discloses the effect of different  $\text{Ca}^{2+}$  channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Other agents that have been shown to interact with T-type channels are mibefradil,  $\text{Mg}^{2+}$  and  $\text{Ni}^{2+}$ . Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the  $\alpha_1$  subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the disclosed result. For example there is no disclosure that  $\text{Mg}^{2+}$  or  $\text{Ni}^{2+}$  can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease associated with interfering with ion channel activity of the  $\alpha_1$  subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with  $\alpha_1$  subunit of T-type calcium ion channel or if antagonists would be beneficial for treatment of said dysfunction. Also, the prior art teaches that the entry of calcium through voltage-dependent  $\text{Ca}^{2+}$  channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on  $\text{Ca}^{2+}$  channels are disclosed throughout the Review Article of Sylvie.

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The utilities asserted by Applicant are not substantial or specific. Neither the specification nor the art of record disclose any disease states treatable by the agonists and antagonists identified by the method of instant invention. Similarly, neither the specification nor the art of record disclose any instances where blocking any effects of T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 would reduce the effect of a disease state. Thus the corresponding asserted utilities are essentially methods of treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use, especially, when the  $\alpha 1$  subunit of the T-type calcium channel encoded by the a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 of the claimed invention is not known. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the disclosed polynucleotides/polypeptides/ agonists/antagonists, further experimentation is necessary to attribute a utility for the method of using the disclosed T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO:23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO:23. See *Brenner v. Manson*, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of

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use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Since the utilities asserted by Applicant for the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23, are not substantial or specific, then it follows that the method of claims 25-31 (method of identifying compounds capable of acting as agonists or antagonists for T-type mammalian calcium channels), also has no utility. No specific disease state has been shown to result from dysfunction of the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23. Similarly, agonists and antagonists identified by said method have no utility in treatment of disease that result from dysfunction of the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23.

A utility to T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23, cannot be assigned without knowledge of what disease is associated with ion channel dysfunction or what drugs/ligands effect a specific function associated with said dysfunction. The superfamily of calcium ion channels is highly divergent in their effects and compound specificity. The utility of  $\alpha_1$  subunits T-type  $\text{Ca}^{2+}$  channels of instant invention cannot be

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implicated solely from homology to known ion channels or their protein domains. The art does not provide any teaching stating that all members of the family calcium ion channels must have the same effects, the same ligands and be involved in the same disease states. The art discloses evidence to the contrary. This specification has used protein domains/homology are predictive as to the activity of the protein. The utility of claimed  $\alpha_1$  subunits T-type  $\text{Ca}^{2+}$  channels cannot be implicated solely from homology to known ion channels or their protein domains because the art does not provide any teaching stating that all members of the family of ion channels must have the same effects, the same ligands, transport the same compound and be involved in the same disease states. The art discloses evidence to the contrary (see above).

Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) "In-depth

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analysis of protein sequences often results in functional predictions not attained in the original studies", page 313, column 2, last paragraph, d) "However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query", page 315, column 2, last paragraph, e) pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi-functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other", page 316. Karp ( Bioinformatics, Vol. 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate

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the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and "Today, what we predict from sequences is at best fragmentary and qualitative", page 332, column 2, second paragraph. Therefore, references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family of  $\text{Ca}^{2+}$  channels, which have very different ligand specificity and functions.

Further, applicants' reference to issued Patents as establishing a patentable utility for the claimed protein is not persuasive because each application is examined on its own merits. In the decision of *In re Hutchison*, 69 USPQ 138 (CCPA, 1946), the court held that

"We are not concerned, of course, with the allowed claims in either the patent or in this application. The sole question for our determination is whether the six article claims on appeal were properly rejected below, and this we pass upon without further reference to, and without comparing them with, the claims in the patent or the claims, which stand allowed in this application."

In essence, the position in the instant application that each application is examined on its own merits can be found in the judicial precedent cited above.

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The rejections in the instant application will only be withdrawn if they are shown to be legally or factually unsound.

In conclusion:

1) The  $\alpha_1$  subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23, 25 or 27 may be full-length subunits. The specification does not teach a person of ordinary skill in the art how to use the specified  $\alpha_1$  subunit in screening assays so that they meet the utility requirements under 35 U.S.C. 101, as indicated above. The specification also does not teach a person of skill in the art how to use the specified  $\alpha_1$  subunit in screening assays so that they meet "how to use" requirement under 35 U.S.C. 112, first paragraph.

2) Publications at the time the priority application was filed do not demonstrate the  $\alpha_1$  subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23, 25 or 27 had a well-established utility, and there was no showing that all agonists and antagonists interacted with all T-type calcium channels. Also there was no showing all agonists and antagonists, or even one could be used to treat diseases of hypertension, stroke, epilepsy, heart disease and cancer.

3) The declaration submitted by Dr. Snutch, has been fully considered by the Office, but it does not demonstrate the claimed screening methods are useful for identifying molecules that treat specific T-type calcium channel related diseases.

4). Due to the facts delineated in items 1, 2 and 3, the screening



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assays do not have a well-established, specific, substantial and credible utility for identifying compounds useful for treating diseases enumerated in the specification.

5) Extensive experimentation is required beyond the claimed processes to identify compounds that treat diseases listed in the specification.

6. Even if the Office already has allowed Patents directed to T-type channels, said Patents cannot be used to establish utility.

Therefore, claims 25-31 remain rejected under 35 U.S.C. 101/35 U.S.C. 112, first paragraph, for reasons of record and those provided above. Claims 25-31 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims remain 25-31 remain rejected under 35 U.S.C. 112, first paragraph (for reasons of record and those provided above). Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax

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phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N/S  
Nirmal S. Basi  
Art Unit 1646  
June 10, 2004

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